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ART UNIT	PAPER NUMBER
1635	

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19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/627,787	Uhlmann
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 21, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above, claim(s) *3, 6, and 7* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4, 5, and 8-26* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Sep 20, 2000* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants amendment received 1/21/03 was entered as Paper No. 18.

Claims 1-26 are pending.

Claims 3, 6, and 7 were withdrawn from consideration in Paper No. 15 as being drawn to nonelected species. Applicant timely traversed in Paper No. 14.

Claims 1, 2, 4, 5, and 8-26 are under consideration in this Office Action.

Election/Restriction

At page 4 of Paper No. 18, Applicant suggests that the Office has a duty to examine the non-elected subject matter to the extent necessary to determine the patentability of the generic claims, relying on MPEP 803.02. However, MPEP 803.02 clearly states that the prior art search "will not be extended unnecessarily to cover all nonelected species". Applicant was advised in Paper No. 15 that upon the allowance of a generic claim, Applicant would be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. In this case no generic claim is allowable, so claims 3, 6, and 7 are not rejoined.

Applicant elected for examination the species of a conjugate comprising an oligonucleotide and aryl radical "F3", wherein the reactive group of the oligonucleotide is a carboxylic acid group. This species was found to be novel and non-obvious, as were each of the species of aryl group recited in claim 9. For this reason, the election of species requirement is

withdrawn for the aryl group. However, the election requirement is maintained with respect to the identity of the compound to be transported, and to the nature of the reactive group. Because the elected species was novel and non-obvious over the prior art, the Office has extended the search to further species of the claimed invention. Claims reciting these species have been found to be anticipated and obvious over the prior art for the reasons given below.

Rejections Withdrawn

The rejection of claims 8, 9, and 24-26 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicant's amendments.

The rejection of claims 1-5, 8, 10, 16-18 and 22-25 under 35 U.S.C. 102(b) as being anticipated by Cook et al is withdrawn in view of Applicant's amendments.

Claim Objections

Claim 9 is objected to because an oxygen has been omitted from structure F4. Compare to F4 in Fig. 2A.

Claims 1 and 12 are objected to because they recite the phrase "reactive function". The claims would be clearer if the word "group" was substituted for the word "function", particularly in view of the language in the Markush group of claim 12 wherein each "function" is identified as a "group." Alternatively, "functional group" could be substituted for "function".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-24 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record, reiterated below.

The claimed invention is drawn to pharmaceutical compositions and methods of making them. The claimed composition is a conjugate of an aryl compound to an oligonucleotide. MPEP 2164.01(c) states:

> When a compound or composition is limited by a particular use, enablement of that claim should be evaluated based on that use.

In this case, enablement of the claimed composition and method must be evaluated in terms of the use of the composition as a pharmaceutical. The specification fails to define the term "pharmaceutical", so in order to understand how this term limits the invention, one must determine its accepted meaning in the art. According to Steadman's Medical Dictionary (26th Edition, 1995) "pharmaceutical" means "relating to pharmacy or to pharmaceutics". In the same dictionary, "pharmacy" is defined as a "practice that emphasizes the therapeutic use of drugs rather than the preparation and dispensing of drugs." Finally, Steadman's Medical Dictionary

defines "drug" as a "therapeutic agent; any substance, other than food, used in the prevention, diagnosis, alleviation, treatment, or cure of disease in man and animal." Thus, to enable a pharmaceutical use for the claimed composition, the specification must teach how to use the substance, without undue experimentation, for the prevention, diagnosis, alleviation, treatment, or cure a disease in the animal to which the substance is administered.

The specification teaches that the claimed compositions can be used for therapeutic and diagnostic purposes *in vivo*. Therapeutic uses of the claimed composition are discussed at page 24, line 29 to page 25, line 2 and page 25, line 27 tp page 26, line 4. The compositions are asserted to be useful for the prevention and treatment of diseases caused by overexpression of certain genes, particularly viral diseases, cancer, restenosis, and depigmentation diseases. See page 25, line 30 to page 26, line 4. Treatment can be effected by delivery of antisense oligonucleotides; triplex-forming oligonucleotides; "decoy" oligonucleotides which mimic the binding site of transcription factors, titrating these factors and inhibiting binding to their natural targets; and chimeraplasts for site-directed gene modification. Thus the claims broadly embrace the treatment or prevention of any disease caused by gene overexpression.

The state of the art with respect to antisense therapies indicates a high level of unpredictability. Crook (In Basic Principles of Antisense Therapeutics, Springer-Verlag, Eds, New York, pgs. 1 and 4), teaches that although antisense techniques have progressed rapidly, "the technology remains in its infancy", and the utility of the approach is still debatable (pg. 1, Introduction). Crook points out several factors which may influence the biological effect of an

antisense oligonucleotide (AODN), including the rate of uptake of the AODN, rate of distribution within the target cell, stability within the target cell, local concentration of the oligonucleotide, and the concentration and stability of the target mRNA (pgs. 1 and 4). Furthermore, Branch (Trends in Biochem Sci 23: 45-50, 1998) teaches that selection of appropriate antisense sequences is difficult because secondary structures of mRNAs *in vivo* frequently restrict access of antisense oligonucleotides to the target sequence (page 45, col. 3. first para., page 48, last para. and page 49). Branch states, "Since accessibility cannot be predicted, rational design of antisense molecules is not possible" (page 49, col. 2, last para.). Ho and Parkinson (Sem. Drug Discov. 24(2): 187-202, 1997) teach that although antisense therapy is simple in theory, it " has proven to be much more complex in practice. A number of important challenges in the preclinical development of antisense oligonucleotides have been identified, including stability, sequence length, cellular uptake, target sequence selection, appropriate negative controls, oligonucleotide: protein interactions, and cost of manufacture." The authors conclude that [c]ontinued progress in this arena will require that many of the preclinical challenges confronting antisense development are satisfactorily resolved." See abstract. Akhtar (J. Antimicrob. Chemother. 38(2): 159-165, 1996) teaches that "a healthy degree of concern exists among scientists and administrators as to whether antisense and, to some extent, ribozyme oligonucleotides will ever become useful therapeutic agents." See page 163, column 1, lines 5-14 of first full paragraph. Thus, at the time the invention was made, there was considerable unpredictability in the design of antisense

oligonucleotides, their delivery and pharmacodynamics, and most importantly, whether or not they would ultimately have any therapeutic value.

Gryzanov (Biochim. Biophys. Acta 1489:131-140, 1999) set forth the state of the art with respect to therapeutic applications of triple helix technology. Gryzanov notes that "several important issues remain to be resolved before oligonucleotides may become widely used unique and specific pharmaceutical agents. Among these are: increased thermodynamic stability of the complexes formed by the oligomers with their nucleic acid targets, specificity of the interactions, resistance to enzymatic degradation and hydrolytic stability in cells, in model animal systems, and importantly, favorable pharmacokinetics and biodistribution in human tissues and organs. Additionally, chemical structures of the therapeutic oligonucleotides, cost of synthesis, and the proper choice of suitable and biologically important molecular targets, as well as delivery methods for administration of compounds, will play a crucial role in ensuring success of oligonucleotide-based therapeutic approaches." See page 132, lines 31-37 of column 1 to line 10 of column 2.

The instant invention addresses the aspect of oligonucleotide (ODN) delivery. The specification indicates that the invention serves to (a) improve delivery by increasing the rate at which ODNs are taken up by cells, (b) circumvent the endocytotic pathway thereby allowing distribution of ODNs to both the cytosol and nucleus, and (c) decrease the damage to cells compared to liposomal delivery compositions. See page 4, line 28 to page 5, line 19. A variety of oligonucleotides designed for the treatment of various diseases is disclosed at pages 13-17. The

specification teaches working examples demonstrating the uptake of the claimed compositions into cultured cells *in vitro*. See Tables 1 and 2 on pages 37 and 38, and also Fig. 9.

The specification does not disclose the effect of the compositions on any cell, or provide any working example of any therapeutic effect. No specific therapeutic or preventative protocol for any disease is taught. No specific guidance is given with respect to dosages or routes of delivery for any particular disease. No evidence is provided that the increased rate of uptake, and improved cellular distribution observed in the instant invention are sufficient to overcome the art-recognized problems associated with therapeutic oligonucleotide delivery as set forth by Crook. The specification fails to account for various critical factors which will influence the success of therapy including the varying concentrations and stabilities of the target mRNAs or polypeptides, the thermodynamic stability of complexes formed by the compositions, the specificity of the interactions, stability of the preparations in animal systems, and pharmacokinetics and biodistribution in human tissues and organs. Perhaps most importantly, none of these issues has been considered within the context of any one therapeutic protocol. Because the physiological art is recognized as being unpredictable (MPEP 2164.03), one of skill in the art recognizes that these variables will change with the identity of the disease to be treated or prevented. However, the specification fails to address the variables cited above in the context of treating or preventing any specific disease. Furthermore, given the unpredictability of oligonucleotide design, as set forth by Branch, it is unclear that any of the oligos taught in the specification will have any therapeutic effect *in vivo*.

Given the unpredictable state of the art of oligonucleotide-mediated therapies, the lack of guidance and working examples in the specification, and the breadth of diseases disclosed as treatable with the claimed compositions, one of skill in the art could not use the claimed invention as intended without undue experimentation.

The specification also teaches that the claimed compositions can be used for *in vivo* diagnosis of diseases caused by the overexpression of genes. See page 24, line 29 to page 25, line 2. However, no guidance is given as to how the claimed compositions may used *in vivo* as a diagnostic. A search of the prior art revealed only two publications related to the *in vivo* use of oligonucleotides for diagnosis, both from the same laboratory. Rusckowski et al (Cancer 80(12)(Supplement): 2699-2705, 1997) and Mardirossian (J. Nucl. Med 38(6): 907-913, 1997) teach the use of oligonucleotides in pretargeting techniques. Briefly, a target entity such as a bacterium or a tumor cell was injected in to the left thigh of a mouse, Then an oligonucleotide, conjugated to a molecule with an affinity for the target entity, was injected into the mouse. Subsequently a complementary, radioactively-labeled oligonucleotide was injected and allowed to hybridize to the first oligonucleotide. Although the resulting signal was detected in the target tissue, it was also associated with liver, heart, kidneys, lung, stomach, spleen, intestines and blood, in amounts greater than in the target tissue. See Rusckowski, Table 1 on page 2702, and Figs. 2 and 3 on pages 2703 and 2704. Clearly the level of false positive signal in these tissues shows that the technique did not have diagnostic value at the time of publication. The instant specification fails to contemplate this specific use for the claimed invention, and thus does not

provide any teachings which would improve the technique to the point that it could function as an *in vivo* diagnostic.

Because the specification provides no guidance as to how to use the claimed invention in vivo as a diagnostic tool, and because the state of the art shows that oligonucleotide compositions were not routinely used for this purpose by those of skill in the art, one of skill in the art would have to perform undue experimentation to use the claimed compositions *in vivo* as diagnostics.

This rejection can be overcome by deleting from the claims the terms "pharmaceutical", "pharmaceutically active", and "pharmaceutical active".

Response to Arguments

Applicant's arguments filed 1/21/03 have been fully considered but they are not persuasive.

Applicant argues generally that:

1) Enablement of the claims does not turn on whether the oligonucleotides of the elected invention have predictable therapeutic effects, and that all that is required is that the specification must teach how to prepare conjugates with greater efficacy than unconjugated compositions. See page 5, paragraphs 2 and 3.

2) The Office provides no evidence that inhibition of tumor growth in vitro cannot be correlated with increased uptake in vivo. See page 7, first paragraph.

3) There is a variety of known pharmaceutically active antisense oligonucleotides. See page 7, paragraph 2.

And

4) Enablement of diagnostic embodiments is proven by the existence of known ex vivo methods.

With regard to item 1), Applicant is reminded that the invention is what is claimed. In this case, what is claimed is a method of making a pharmaceutical composition comprising preparing a pharmaceutically active compound. In the elected invention, the pharmaceutically active compound is an oligonucleotide, therefore the claims require pharmaceutically active oligonucleotides and enablement must turn on whether or not the specification adequately teaches how to make and use them.

With regard to item 2), it is not the Examiner's burden to provide evidence that inhibition of tumor growth in vitro cannot be correlated with increased uptake in vivo. Rather, the relevant correlation is that between the in vitro model and any in vivo therapeutic result. MPEP 2164.03 indicates that the examiner must give reasons for any lack of correlation between vitro data and expected in vivo results. The primary reasons for a lack of correlation are discussed by Crooke, Akhtar, and Gryzanov above, and generally relate to the differences of in vivo and in vitro systems particularly with respect to pharmacokinetics and biodistribution and the unpredictability that arises therefrom. When considered in light of the tremendous breadth of diseases that the specification discloses as treatable by the claimed invention, and the failure to provide an in vivo working example, the reasons given for a finding of a lack of enablement are considered to be sufficient.

Applicant argues that the "how to use requirement" of U.S.C. 112, first paragraph for in vivo therapy can be satisfied by demonstration of pharmacological activity in vitro, and relies for support upon *Cross v. Iizuka* and *In re Brana*. However, in *Cross v. Iizuka*, the court did not find that the "how to use requirement" for in vivo therapy can be satisfied by demonstration of pharmacological activity in vitro. The enablement issue in *Cross v. Iizuka* was strictly limited to determining in vitro efficacy. The court found that the disclosure was enabling for determining I_{C50} in an in vitro microsomal system, and clearly stated that the issue under consideration was pharmacological activity in vitro and not therapeutic use in vivo. See 224 USPQ at page 748.

> The Board found that there was sufficient credible evidence that one skilled in the art, without the exercise of inventive skill or undue experimentation, could determine the IC_{50} dosage level for the imidazole derivatives of the phantom count in the microsome environment. Cf. Bundy, id., 209 USPQ at 51. We do not believe the Board erred in arriving at this conclusion. **This is not a case such as In re Gardner, 427 F.2d 786, 166 USPQ 138 (1970), where the CCPA held that the applicant's disclosure was nonenabling because inventive skill and undue experimentation would be required to discover appropriate dosages for humans, i.e., a therapeutic use. In the instant case, we are confronted with a pharmacological activity or practical utility, not a therapeutic use.**

Emphasis added. Furthermore, even if *Cross v. Iizuka* did support the correlation between in vivo and in vitro results, it is not analogous to the instant invention. In *Cross v. Iizuka*, the issue was enablement of inhibitors of thromboxane synthetase, not therapeutic oligonucleotides. The standard and practice for testing thromboxane synthetase inhibitors was well settled at the time of filing, and the correlation between structural and functional of the inhibitors was well characterized, so unpredictability was not as great an issue as in the instant case. Here, the Office has established that the arts of oligonucleotide-mediated therapy and diagnosis are highly unpredictable. See Crooke, Branch, Ho, Akhtar, Gryzanov, Rusckowski, and Mardirossian

above. This line of reasoning applies also to applicants reliance on *In re Brana*, i.e. the fact that those of skill in the art recognize that the application of antisense therapy in vivo is complicated by a variety of factors that are absent in vitro, discussed above and in Paper No. 17 in response to Applicant's arguments. Cell culture examples of antisense techniques are generally not predictive of in vivo results due to differences in metabolites and clearance rates, local concentration of antisense, differences in target site accessibility, cellular uptake differences and the potential for non-antisense side effects. Often formulations and techniques for delivery in vitro (cell culture) are not applicable in vivo (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see pages 79-80, section entitled Cellular uptake facilitators for in vitro studies) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides. In vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell in vitro versus in vivo, the uptake and biological activity observed in vitro would not predictably translate to in vivo results.

The field of antisense, to date, does not provide guidelines by which antisense can be routinely delivered to generally any cell type in vivo (whole organism) at a concentration effective to result in a predictable therapeutic effect. The specification does not provide specific guidance

by which one skilled in the art would expect to be able to deliver antisense targeted to sphingosine-1-phosphate lyase to generally any target cell or tissue in vivo (whole organism) at a concentration effective to provide a pharmaceutical effect or to treat the broad range of diseases encompassed by the claims.

In order to practice the invention claimed over the full scope claimed, i.e. the production of a *pharmaceutical* composition, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include the determination of what specific diseases and conditions can be treated by the administration of any antisense oligonucleotide, what specific cells to target with antisense for the treatment of a particular disease or condition, and how to specifically deliver antisense to a target cell in vivo (whole organism) at a concentration effective to result in inhibition of the expression of a target gene to a level sufficient to result in a pharmaceutical effect or to treat a disease. Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half life and stability of the antisense molecule in vivo. Given the art recognized unpredictability of the therapeutic application of antisense in vivo (whole organism), this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the broad scope embraced by the claims, the state of the art of antisense and triplex technologies, the level of unpredictability of in vivo (whole organism) methods of treatment using antisense, the lack of specific guidance for the in vivo (whole organism)

application of antisense methods of treatment and the lack of working examples or examples which correlate with the claimed methods, one skilled in the art would not be able to practice the invention over the full scope claimed without undue trial and error experimentation.

With regard to item 3), Applicant's assertion that there is a variety of pharmaceutically active oligonucleotides known in the art is unsupported by evidence. Applicant has not provided an example of any of the patents asserted to have been issued, and so the evidence is considered to be hearsay. Further, Applicant is advised that should such evidence be furnished, the enablement of each application is considered on its own merits, so it is not immediately clear that such evidence would show that the instant disclosure is enabling.

Applicant asserts that the Office seems to require success in clinical trials before a compound can be "pharmaceutically active". The Office makes no such requirement. In response to Applicant's arguments that the instant invention must be enabled because clinical trials of antisense oligos were in progress, the Office merely pointed out that this was not evidence of enablement, particularly in view of the unpredictability of the art and the breadth of the claims in view of the specification. It si well known, and apparent from the teachings of Dove (2002) , that some products in clinical trials are shown to have therapeutic utility, whereas some products are known to have therapeutic utility prior to clinical trials. In this case, the specification fails to disclose any example of a therapeutic oligonucleotide.

With regard to item 4), Applicant's arguments that it is preferable to perform diagnostic procedures ex vivo or in vitro when possible are misplaced. The issue is whether or not the

specification enables diagnosis through the delivery of the compositions in vivo, not ex vivo, or in vitro. One of skill in the art would not go to the trouble of making a pharmaceutically acceptable reagent for use ex vivo or in vitro. The use of the term "pharmaceutical" is taken to imply that the composition is to be used in vivo for the treatment or diagnosis of disease..

For these reasons the rejection is maintained.

The rejection can be overcome by deleting from the claims the terms "pharmaceutical", "pharmaceutically active", and "pharmaceutical active".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 5, 10, and 22-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Radhakrishnan et al (Bioorg. Med. Chem. 7(7): 871-876, 1997).

Radhakrishnan teaches bioreversible conjugates for delivery of oligonucleotides to cells. The conjugates comprise an aryl radical according to instant claim 1 bound to an oligonucleotide by an internucleotide phosphodiester bond. The conjugates may be delivered to cells for diagnostic purposes and subsequently cleaved by cellular esterases to release the oligonucleotide.

See page 871, lines 1, 10-12, and Fig. 1; and page 872, Fig. 2. Pertinent to claim 5, the oligonucleotide is considered to be modified by the addition of the aryl radical. Radhakrishnan teaches a method of making the conjugate in which a derivative of the oligonucleotide, a mononucleotide, is prepared and reacted with the aryl radical. See Scheme 1 on page 872. Pertinent to claim 23, the resulting conjugate is then admixed with other nucleotides in the process of building the oligonucleotide. It is noted that, while the compositions of Radhakrishnan are not considered to be enabled for pharmaceutical use, they are structurally indistinguishable to the compounds of claim 24, so this claim is properly rejected.

Thus Radhakrishnan anticipates the claims.

Claims 11, 12 and 15 stand rejected under 35 U.S.C. 102(b) as being anticipated by Cook et al (WO94/01448, published 1/20/94) for the reasons of record in Paper No. 17, reiterated below.

Cook teaches oligonucleotides covalently linked to a variety of moieties, including an aryl conjugate which comprises an X-(C=Y)-R1 group and processes for preparing them. See abstract; and page 6, line 4, second structure. The compounds may be transferred across the cell membranes of bacterial cells, or human tumor cells. See e.g. list of targets in the table bridging pages 18 and 19 particularly lines 5 and 11 on page 19.

Thus Cook anticipates the claims.

Claims 1, 2, 8, 24, and 25 are rejected under 35 U.S.C. 102(a) as being anticipated by Cuthbertson et al (WO 99/55383, published 11/4/99).

Cuthbertson teaches compositions comprising conjugates comprising an aryl radical according to instant claims 1 and 8 bound to a polypeptide. See e.g. Fig. 3, bottom two structures. Cuthbertson teaches that the compositions may comprise therapeutic or diagnostic agents. See abstract.

Thus Cuthbertson anticipates the claims.

It is noted that Cuthbertson was published after 7/28/99, the date to which Applicant claims benefit. In order to overcome this rejection, Applicant must perfect the filing date of the foreign priority document (DE 199 35 302.6). The filing date of the priority document is not perfected unless applicant has filed a certified priority document in the application **(and an English language translation, if the document is not in English)** (see 37 CFR 1.55(a)(3)) and the examiner has established that the priority document satisfies the enablement and description requirements of 35 U.S.C. 112. See MPEP 706.02(b)(E). In this case, no English language translation of the priority document has been filed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11, 13, and 14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Cook et al (WO94/01448, published 1/20/94) for the reasons of record in Paper No. 17, reiterated below..

Cook teaches oligonucleotides covalently linked to a variety of moieties, including an aryl conjugate which comprises an X-(C=Y)-R1 group and processes for preparing them. See abstract; and page 6, line 4, second structure. The aryl group may be attached to an amino reactive group, e.g. N6 of adenine. See page 4, last sentence. The compounds may be transferred across the cell membranes of bacterial cells, or human tumor cells. See e.g. list of targets in the table bridging pages 18 and 19 particularly lines 5 and 11 on page 19.

Cook is silent as to the pH at which the synthesis reaction must be carried out.

It would have been obvious to one of ordinary skill in the art at the time of the invention to perform the reaction at pH 7 because the pH at which a reaction is performed is a result effective variable that is routinely optimized. Generally, differences in concentration of reactants, such as hydrogen ions, should not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that this concentration is critical. See MPEP 2144.05(b). "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454 105 USPQ 233, 235 (CCPA 1955). In this case, the pH is not disclosed as critical.

In any event, Cook teaches the formation of the same chemical structure, using the same required reactive group (an amine group), thus one would reasonably expect that the optimal pH of the reaction of Cook would be similar to that of the instant invention.

Thus the invention as a whole was *prima facie* obvious.

Claims 16-19, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peyman et al (US Patent 6,013,639, issued 1/11/00) in view of Radhakrishnan et al (Bioorg. Med. Chem. 7(7): 871-876, 1997).

Peyman teaches a method of delivering to tumor cells a diagnostic oligonucleotide conjugated to a C12-C22 alkyl chain. See abstract, column 4, line 61 to column 4, line 5, and claim 45 at column 52.

Peyman does not teach an aryl linkage of formula I.

Radhakrishnan teaches bioreversible conjugates for delivery of oligonucleotides to cells. The conjugates comprise an aryl radical according to instant claim 1 bound to an oligonucleotide by an internucleotide phosphodiester bond. See page 871, lines 1, 10-12, and Fig. 1; and page 872, Fig. 2.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the composition of Peyman by providing the aryl linkage of Radhakrishnan, because Radhakrishnan teaches that oligonucleotide conjugates may have reduced affinity for their targets, and the linkage of Radhakrishnan is labile to cellular esterases. Thus one would have been

motivated to modify the composition of Peyman in order to obtain improved affinity of the oligonucleotide for its target sequence, and the invention as a whole was prima facie obvious.

Claim 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al (US Patent 6,080,580, issued 6/27/00) in view of Peyman et al (US Patent 6,013,639, issued 1/11/00) and Radhakrishnan et al (Bioorg. Med. Chem. 7(7): 871-876, 1997).

Baker teaches methods of delivering lipidic oligonucleotide conjugates to human cells. The lipidic group may be cholesterol. See column 9, lines 55-61; and claim 11 at column 150.

Baker does not teach an aryl linkage of formula I, or a C1-C23 alkyl radical that is straight chain or branched.

Peyman teaches a method of delivering to tumor cells an oligonucleotide conjugated to a lipophilic group which may be a C12-C22 alkyl chain or cholesterol. See abstract, column 4, line 61 to column 4, line 15, and claim 45 at column 52.

Radhakrishnan teaches bioreversible conjugates for delivery of oligonucleotides to cells. The conjugates comprise an aryl radical according to instant claim 1 bound to an oligonucleotide by an internucleotide phosphodiester bond. See page 871, lines 1, 10-12, and Fig. 1; and page 872, Fig. 2.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the composition of Baker by providing the aryl linkage of Radhakrishnan, because Radhakrishnan teaches that oligonucleotide conjugates may have reduced affinity for their targets,

and the linkage of Radhakrishnan is labile to cellular esterases. Thus one would have been motivated to modify the composition of Baker in order to obtain improved affinity of an oligonucleotide for its target sequence, and the invention as a whole was prima facie obvious. It would have been obvious to substitute the C12-C22 alkyl chain of Peyman for the cholesterol of Baker because Peyman teaches that these groups may substituted for one another as lipophilic groups that facilitate cell penetration. See column 4, line 61 to column 4, line 15. MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Also, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was prima facie obvious.

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Radhakrishnan et al (Bioorg. Med. Chem. 7(7): 871-876, 1997).

Radhakrishnan teaches bioreversible conjugates for delivery of oligonucleotides to cells. The conjugates comprise an aryl radical according to instant claim 1 bound to an oligonucleotide by an internucleotide phosphodiester bond.

Radhakrishnan does not explicitly teach organization of the conjugate into a test kit.

It would have been obvious to one of ordinary skill in the art at the time of the invention to organize the conjugate into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

Thus the invention as a whole was prima facie obvious.

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cuthbertson et al (WO 99/55383, published 11/4/99).

Cuthbertson teaches compositions comprising conjugates comprising an aryl radical according to instant claims 1 and 8 bound to a polypeptide. See e.g. Fig. 3, bottom two structures. Cuthbertson teaches that the compositions may comprise therapeutic or diagnostic agents. See abstract.

Cuthbertson does not explicitly teach organization of the conjugate into a test kit.

It would have been obvious to one of ordinary skill in the art at the time of the invention to organize the conjugate into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant argues at pages 9-12 that Cook fails to anticipate claims 11, 12, and 15, or render obvious claims 13, and 14, because Cook does not teach the amended version of R1 set forth in claims 1 and 8. This is unpersuasive because claims 11, 12, and 15 do not depend from claims 1 or 8, and do not recite Formula I, Formula II, or any limitation pertaining to an R1 group. Applicant further argues that Cook teaches a wide variety of conjugates, and that in order to make a case of prima facie obviousness, the Office must show that the broad disclosure of Cook would lead one of skill in the art to the presently claimed genus of compositions. This is unpersuasive because claims 11, 12, and 15 are anticipated, not merely obvious, in view of Cook. Applicant has failed to address the basis of the obviousness rejection of claims 13 and 14, which is related to the optimization of reaction conditions, i.e. pH. For these reasons the rejections are maintained.

Conclusion

No claim is allowed. Claim 9 is free of the prior art of record and is objected to because it depends from a rejected claim. Claim 9 would be allowable if rewritten in independent form incorporating all the limitations of the rejected claim, and if the objection at page 3 of this Action is appropriately addressed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

a shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This application contains claims **3, 6, 7, and 9** which recite species nonelected with traverse in Paper No.14. A complete reply to the final rejection must include cancellation of nonelected species or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit

1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER